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Say no to cyanokit. Pause at the 10, 10 threshold

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Dear Dr. Wolf:

Cyanide is ubiquitous in the environment and can be released as hydrogen cyanide gas in smoke. Cyanide toxicity is considered when patients present with smoke inhalation, and its rapid onset of action, combined with limited testing, leads many to empirically treat. As of 2016, Cyanokit (hydroxocobalamin) is available in the US and the European Union for treatment of cyanide poisoning, and its use has become widespread in the hospital and prehospital setting. Less appreciated is the adverse effect of Cyanokit administration —renal failure. Cyanokit administration is associated with a 60% increased risk of acute kidney injury (AKI) of any form and nearly triples the risk of severe AKI requiring renal replacement therapy [1]. The exact mechanism is unclear; however, histologic evidence suggests that hydroxocobalamin leads to the formation of oxalate crystals in renal tubules which precipitate renal failure [2]. There is currently no guideline in the United States for whom Cyanokits should be given other than a suspicion for cyanide poisoning. The widespread availability of Cyanokit in multiple care settings, as well as the low threshold of "suspected inhalation" for administration, may lead to large numbers of patients at risk of receiving the medication. The burn community and any provider caring for smoke inhalation patients should have sound justification for using Cyanokits while simultaneously considering adverse effects. Regardless of the precise risk of renal failure with Cyanokit use, as more Cyanokits are administered, the absolute number of patients with attributable renal

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All authors have made significant contributions to this manuscript including: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted. We confirm that this manuscript has not been published elsewhere and is not currently under consideration by another journal. If accepted, the paper will not be published elsewhere in the same or similar form. We also have no financial disclosures or conflicts of interest to report.

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failure will increase. We propose a reasonable threshold for administering Cyanokits based on evidence and modern understanding of cyanide poisoning pathophysiology.

Smoke inhalation commonly results from persons being trapped inside structure fires. Of all structural components, wood generates the greatest volume of smoke and yields both complete and incomplete products of combustion [3]. The most aerosolized molecules include H_2O, CO, CO_2, formaldehyde, and acrolein. All organic matter contains some amount of nitrogen which can form hydrogen cyanide when combusted, but there is no evidence that wood combustion generates significant amounts of any cyanide gas. On the other hand, plastic, vinyl, wool, silk and organic fuels (i.e. petroleum) may undergo pyrolysis with heat yielding voluminous amounts of cyanide gas. Of all household materials, wool yields the greatest amount of hydrogen cyanide at 6300 micrograms per gram combusted [4]. Thus, knowledge of the contents of a structure fire gives clinicians and first responders better estimates of likelihood of cyanide exposure and should be factored into the decision of whether to administer Cyanokit when known.

CO poisoning is easily detectable using modern CO-oximetry devices and laboratory testing. Within minutes, first responders determine whether a patient has life threatening blood concentrations of HbCO which can alert providers to consider concomitant cyanide poisoning. If considering cyanide poisoning because of a structure fire, HbCO levels are a reasonable surrogate for the quantity of smoke inhaled, and thus the likelihood of cyanide poisoning. Various studies are shown a relationship between HbCO and cyanide levels. Many facilities are unable to measure cyanide levels, and those with ability take hours to return which precludes meaningful decision making. Based on largest series of observational data with cyanide and HbCO levels, the mean HbCO in cyanide toxicity was 62.5% with no cases less than 11.3% [5].

In addition to HbCO levels, serum lactate provides another useful test in determining the likelihood of cyanide toxicity. Cyanide binds to cytochrome A3 of the inner mitochondrial membrane arresting oxidative phosphorylation and generation of ATP. Thus, even with plenty of oxygen available, anaerobic metabolism is forced because cells cannot oxidize oxygen. Lactate generation ensues and can easily be measured with point of care testing. Similar to studies correlating HbCO levels with cyanide toxicity, lactate similarly shows a relationship such that levels in excess of 10 mmol/l are suggestive of cyanide toxicity with both high sensitivity and specificity [6].

Isolated cyanide gas inhalation without smoke inhalation rarely occurs and would be a purposeful act of suicide or homicide. Clear history would distinguish this scenario along with altered/depressed mental status and laboratory values suggesting a severe lactate acidosis. It goes without saying that any provider who has significant suspicion for cyanide toxicity should administered a Cyanokit regardless of laboratory values or anticipated effects on renal function. Saving the brain and heart is more important than saving the kidneys. That said, a prudent approach to Cyanokit administration using the HbCO and lactate thresholds of 10% and 10 mmol/L may also prevent kidney injury in patients who otherwise do not have cyanide poisoning (Fig. 1).

It is reasonable then to propose a guideline for Cyanokit administration based on mental status, lactate and CO levels. Patients with normal mental status, and a HbCO level< 10% should not receive treatment with Cyanokit. Treatment should be reserved for those with cardiac arrest, GCS< 10 and lactate> 10 mmol/L and HbCO levels> 10%. Taking a more prudent approach will allow appropriate treatment, minimize risk to those without significant exposure, and reduce the costs of Cyanokit utilization.

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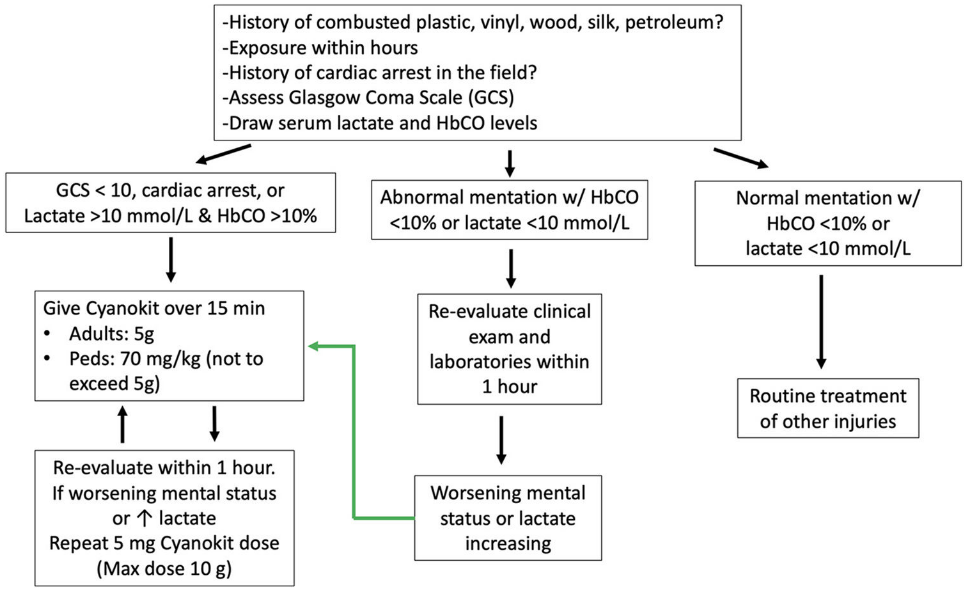

Fig. 1 –.

Algorithm for consideration of Cyanokit administration using lactate, HbCO, and mental status.